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Scientists unravel role of fusion gene in prostate cancer

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Up to half of all prostate cancer cells have a chromosomal rearrangement that results in a new "fusion" gene and formation of its unique protein -- but no one has known how that alteration promotes cancer growth. Now, Weill Cornell Medical College researchers have found that in these cancer cells, the 3-D architecture of DNA, wrapped up in a little ball known as a chromatin, is warped in such a way that a switch has been thrown on thousands of genes, turning them on or off to promote abnormal, unchecked growth. Researchers also found that new chromosomal translocations form, further destabilizing the genome.

These findings, published in the Proceedings of the National Academy of Sciences (PNAS), are the first to show how this chromosomal mutation likely contributes to early development of prostate cancer -- and suggests a model for how other chromosomal translocations, common to many tumor types, are linked to cancer formation and growth.

"This is likely a phenomenon that occurs in many types of cancers when oncogenic fusion genes are over-expressed," says the study's senior author, Dr. Mark A. Rubin, The Homer T. Hirst Professor of Oncology in Pathology and vice chair for experimental pathology at Weill Cornell Medical College.

Dr. Rubin adds that if such an oncogenic protein has the power to throw the switch on thousands of genes, a novel treatment may be able to turn that switch off. "If we understand how this works, then we may be able

to borrow that trick to target many genes simultaneously. This discovery would hold a lot of promise for cancer therapy," he says.

The study also adds to the growing understanding of how remodeling of the chromatin regulates genes linked to cancer, says the study's lead author, Dr. David S. Rickman, assistant professor of pathology and laboratory medicine at Weill Cornell Medical College. The genome's DNA, along with specialized proteins, has to be packed into the chromatin bundle so that it can fit inside a cell's nucleus, and when genes need to be expressed, the chromatin opens up a bit, allowing transcription. Emerging evidence suggests that, within this package, the genome organizes itself according to a non-randomly-assembled, 3-D architecture of hubs and domains that affect when and where individual genes are turned on.

This study shows the oncogenic ERG protein, produced by the ETS prostate cancer fusion gene, binds to specific sites in the genome, which then forces the 3-D genome architecture to vastly change, creating different hubs and domains, Dr. Rickman says. This results in additional chromosomal translocations, as well as a coordinated expression of genes known to be relevant to aggressive prostate cancer, he says.

The research shows just how complex genetic regulation really is and how distortions in this process can lead to cancer, says Dr. Rubin, who is also a professor of pathology and laboratory medicine and professor of pathology in urology at Weill Cornell Medical College.

"We used to think everything related to gene expression was linear, that one promoter affected the gene located right next to it," he says. "Now we are beginning to understand that what happens in the 3-D space of tightly bundled DNA is also important -- how DNA opens up and undergoes changes that efficiently turn on whole sets of genes that aren't located anywhere near each other."

It Takes a Village -- of Scientists

Reaching these findings required a collaborative team of scientists, says Dr. Rubin, who co-discovered the ETS fusion gene. For this project, he sought the expertise of Dr. Rickman and Dr. Olivier Elemento, an assistant professor in the Department of Physiology and Biophysics and assistant professor of computational genomics in the Institute for Computational Biomedicine at Weill Cornell Medical College, and a co-senior author of the paper. Dr. Elemento and his lab provided the expertise in computational biology and mathematical analysis needed to interpret the complex data produced by the experiments run by Dr. Rickman, his lab and members of the Rubin laboratory.

Joining them were nine other scientists from Weill Cornell Medical College, and two from Mount Sinai School of Medicine.

Dr. Elemento, Dr. Rickman and their laboratory colleagues used numerous techniques to understand the effect of the ERG oncoprotein. They first used an experimental technique called Hi-C to query chromatin interactions throughout the genome. "Chromatin interactions are inherently complex and it is easy to grasp why this is so," says Dr. Elemento. "There are about 25,000 known genes in the human genome therefore there are possibly 25,000 x 25,000 interactions between genes -- which is 625 million -- and that is only scratching the surface."

To treat the high volume of data the researchers needed to develop new statistical methods to detect chromatin interactions and the changes that occur when ERG is over-expressed.

Then, to understand why these chromatin interaction changes occurred in the first place -- what it is that ERG does to generate new interactions or abolish existing ones -- they performed additional experiments, which produced even more data. They used a technique called ChIP-seq to map

where on the genome ERG likes to bind, and then used the RNA-seq tool to determine which genes are expressed or shut down when ERG is present.

More analyses were needed to identify genes and regions on the genome whose interaction patterns changed most when ERG was over-expressed. Finally, they reached what Dr. Elemento called a shocking revelation: "ERG binds very often near the genes whose interaction patterns change the most, thus indicating that ERG directly mediates the interaction by binding to these regions."

The researchers then discovered that genes whose expression was collectively increased or shut down, and which were involved in chromatin interactions, were those that are involved in cell invasion, a key feature of aggressive prostate cancer. "We thus think that ERG may contribute to prostate cancer phenotype by rearranging chromatin interactions to promote the expression of these key malignancy genes," Dr. Elemento says.

ERG also seems to push the formation of new chromosomal translocations, he says. "This is exciting because it points to a completely novel, non-transcriptional role for ERG in cancer," Dr. Elemento says. "We think that it is possible that many genes like ERG -- which bind to the DNA -- could promote the formation of novel genetic alterations by rearranging chromatin interactions."

Dr. Rickman agrees, "These findings extend beyond the context of the prostate as many driving genetic lesions in other cancer types involve abnormal expression of transcription factors due to genomic alterations."

The researchers are now conducting studies to unravel the mechanism that accounts for these architectural changes. "Achieving this will provide a new understanding of cancer and novel ways to treat and

prevent its progression," Dr. Rickman says.

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